

REMARKS

Pursuant to this paper, claims 1, 3, 5, 19-22, 26, 85, 86, 88-91, 106, 107, 110, 112 and 117-119 will be pending and under examination. Claims 117-119 are new.

Elected claims 4, 6-10, 14, 18, 23-25, 83, 84, 87, 93, 94, 96-105, 108, 109, 111 and 113-116 and presently withdrawn claims 2, 4, 15-17, 27-29, 75-78 and 81 are canceled herein without prejudice.

Claims 1, 3, 5, 12, 13, 19-22, 26, 85, 86, 88, 110 and 112, are amended as shown in the listing of claims beginning on page 2 of this paper. The amendments of the claims limit the recited invention to more narrowly surround the commercial embodiments of the invention.

Support for the amendment of each of claims 1 and 3 is found in the originally filed specification ("o/f/s") as follows: Support for 30-80 mg/ml at page 21, ll. 4-8 of the o/f/s. Support for 10-60 mg/ml concentration limitation found in now-canceled, originally filed Claim 6). Support for the polysorbate limitation is found in claim 101. Support for mannitol or sorbitol limitation is found at page 19, ll. 22-24 of o/f/s.

Claim 5 is amended to agree with its base claim 1.

Support for the amendment of claim 12 (PVP limitation) is found at page 15, ll. 4-5 of the o/f/s. Support for the amendment of claim 13 is found at page 15, ll. 4-5 of the o/f/s and the same aforementioned support for the amendment of claims 1 and 3.

Claims 19-21 are amended to agree with the language of base claim 1. Claim 22 is amended to more clearly recite the invention.

Each of claims 85, 86 and 88 is amended to agree with amended claim 1 and the dependency of claim 88 is changed to be dependent on claim 1.

Claim 110 is amended to more clearly recite what Applicants regard as the invention.

Support for new claims 117 and 118 is found in prior version of claim 1 (concentration limitation), prior claim 101 (polysorbate limitation), page 19, ll. 22-24 of the originally filed specification (sorbitol or mannitol limitation), in claim 8 and at page 21 ll. 4-8 of the o/f/s (water as carrier), originally filed claim 7 and also at page 2, ll. 12-15 (colloidal dispersion), and page 2, ll. 12-15 of the o/f/s (diameter limitation). Support for new claim 119 is the same, adding the PVP limitation having support at page 15, ll. 4-5 of the o/f/s. Claims 117 and its dependent claims 118 and 119 are parallel to claim 1 and its dependent claims 3 and 13, but recite a different range of concentration of active ingredient.

No new matter has been added by any of the amendments made herein.

1. SUMMARY OF EXAMINER INTERVIEW

Applicants thank the Examiner for the telephonic interview conducted with the undersigned Attorney for Applicants on July 8, 2009. The undersigned and the Examiner discussed the following during the interview: (1) the advantages of the commercial embodiment of the invention called "Ryanodex" as shown in Gerbershagen et al., Comparison of Therapeutic Effectiveness of Dantrolene and Ryanodex in Porcine Malignant Hyperthermia, Anesthesiology, 2007; 107: A1922 (Abstract of ASA Meeting, *of record*, disclosed in IDS filed December 12, 2008); and (2) a set of proposed claim amendments limiting the recited subject matter of the claims to more narrowly surround the commercial embodiment (Exhibit A to this paper).

It is believed that the undersigned and the Examiner came to agreement that the "liquid formulation" claims of the proposed amendment are allowable, while the dry formulation claims and method-of-preparation claims could not be allowed in their proposed form because the physical form of the "dry form" recited in those claims was not described with sufficient particularity.

Accordingly, the liquid formulation claims are amended herein as was proposed in the interview, while the dry formulation claims and the method-of-preparation claims are canceled without prejudice in order to facilitate the examination and allowance of the instant application.

2. THE AMENDED CLAIMS ARE NOVEL

Claims 1, 3, 5-8, 10, 12, 14, 18-26, 83, 84, 87-91, 93, 94, 96-100, 102-105, 108, 109 and 112-116 were rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Karan et al., Anesth Analg 82: 796-802, 1996 ("Karan," *of record*). (Office Action, ¶¶3-6.)

The present rejection of the claims is overcome for the following reasons.

First, the present rejection has been rendered moot with respect to claims 6-8, 10, 12, 14, 18, 23-25, 83, 84, 87, 93, 94, 96-100, 102-105, 108, 109 and 113-116 due to their cancellations herein.

Second, with respect to the remaining claims, each of independent claim 1 (as amended) and 117 (newly added), recites preferred liquid formulations of the invention containing dantrolene sodium particles of specified size in combination with a water soluble polysorbate

and sorbitol or mannitol. The combination of elements now recited in the independent claims is not disclosed by Karan. Thus, Karan does not anticipate the presently amended claims.

In view of the above, withdrawal of the present rejection of the claims under 35 U.S.C. § 102(b) is hereby requested.

3. THE PRESENTLY CLAIMED INVENTION IS NON-OBVIOUS

(A.) Claims 1, 3, 5-10, 12-14, 18-26, 83-91, 93, 94, and 96-116 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,543,359 to Ellis et al. ("Ellis"), in view of U.S. Patent No. 6,294,192 to Patel et al. ("Patel"), U.S. Patent No. 6,495,164 to Ramstack et al. ("Ramstack"), U.S. Patent No. 5,510,118 to Bosch et al. ("Bosch") and the Karan reference. (Office Action, ¶¶2-7.)

The present rejection of the claims is overcome for the following reasons.

(i.) The prior art teaches against the invention recited in the presently amended claims and shows that the art is unpredictable

The presently amended claims are specifically directed to preferred embodiments of the invention in which the form of dantrolene is sodium (Na) dantrolene particles. (See amended claim 1 and new claim 117.) However, Karan specifically investigated both neutral (MC-D) and sodium (MC-NaD) formulations of dantrolene and explicitly found the sodium dantrolene formulation to be disfavored and inferior. Specifically, Karan teaches:

MC-NaD caused **marked** pulmonary hypertension in swine, while MC-D caused only a mild response that was eliminated by filtration.

(Karan, Abstract; emphasis added.)

[T]he MC-D formulation has greater potential to improve the pharmacologic treatment of MH due to its safety profile.

(Karan, pg. 801, L-col., ll. 7-9; *as compared to MC-NaD*.)

In theory, filtration should remove the larger particles that can be present as a byproduct of the manufacturing or reconstitution process. However, filtration was not successful in eliminating the pulmonary response of MC-NaD in swine. Further, observations at 200 X dilution showed a tendency for aggregation even after filtration.

(Karan, pg. 801, R-col., ll. 3-9.)

Thus, the actual experimental results of Karan and the conclusions drawn from them therein would teach a skilled worker in the art to specifically avoid using a sodium dantrolene form of dantrolene in a low-volume, high-concentration formulation of dantrolene. Moreover, the Karan reference shows how unpredictable the art is. Based on this art, one could not predict that a usable low-volume, high-concentration formulation of sodium dantrolene could be obtained or how to obtain it. Instead the art teaches that is *cannot* be obtained. Despite this, it is Applicants who have discovered a superior formulation which is, in fact, uses a sodium form of dantrolene.

Further, Applicants wish to point out that Patel has as its core teaching the use of *both* a hydrophilic surfactant and a hydrophobic surfactant. This would clearly lead a skilled worker away from the presently claimed invention and, further, this possibility is explicitly excluded by the language of claims 3, 13, 118 and 119.

(ii.) A *prima facie* case for obviousness has not been made out because the required “reasonable expectation of success” is not present

The state-of-the-art is that what is desired, namely a rapidly administrable, high-concentration, intravenous-safe dantrolene formulation, is not available and nowhere to be found except in presently claimed invention which narrowly surrounds the commercial *sodium dantrolene* embodiment of the invention described in Gerbershagen et al. (*of record*). Indeed, if it were obvious to prepare a usable high-concentration formulation from a combination of the cited references were obvious, workers in the field would have long ago have produced it and brought it to the clinic given the lives that would be saved and the substantial financial reward that would be involved. Further, no evidence supporting the existence of a reasonable expectation of success in obtaining the presently claimed invention by combining the cited references has been presented, *especially* given the present limitation of the claims to *sodium* dantrolene and Karan’s teaching against it – instead, all of the experimental evidence is against there being a reasonable expectation of success.

(iii.) The asserted rejection employs an improper degree of hindsight

Even assuming, *in arguendo*, that the cited references contain the various elements needed to construct the presently claimed invention, the degree of picking-and-choosing required

to make the invention is so extreme that no skilled worker would be so guided without the benefit of the present disclosure. While the Courts have suggested that *some* degree of hindsight is permissible in making a finding of obviousness, Applicants respectfully submit that an extreme and impermissible degree of hindsight relying almost exclusively on the guidance provided by the instant specification has been employed, and would have to be employed, to selectively pick out the disparate steps cited from the recited references and arrange them in a manner approximating the presently claimed invention. How would any skilled worker know or be guided to create the particular formulation of the presently claimed invention based only on the references? It is not enough for obviousness that among thousands of possible permutations of combinations of elements from numerous references may lay a claimed invention. See In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009)(The Court found that obvious-to-try was an improper standard where what would have been allegedly obvious to try was to vary all parameters or try each of numerous possible choices until arriving at a successful result where the prior art gave either no indication of critical parameters or any other direction as to which of many possible choices was likely to be successful.) To wit, given the teachings of the cited references a skilled worker would not be guided to the presently claimed invention over any other of the multitude of permutations.

In view of the above, Applicants respectfully request withdrawal of the present rejection of the claims under 35 U.S.C. §103(a).

(B.) Claims 1, 3, 5-10, 12-14, 18-26, 83-91, 93, 94, and 96-116 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over the Karan reference in view of U.S. Patent No. 5,922,355 to Parikh et al. ("Parikh"). (Office Action, ¶¶8-11)

The present rejection of the claims is overcome for the following reasons.

The teachings of Karan are discussed in subsection (A.) above and incorporated by reference here, including in pertinent part that the formulations of that reference are based on lecithin (a phospholipid; see Lecithin, Wikipedia entry, instant IDS; "*lecithin* is sometimes used as a synonym for pure phosphatidylcholine") and the teaching against use of the *sodium* dantrolene formulation. Polysorbate as recited in the instant independent claims is not a phospholipid. Parikh exclusively teaches formulations which necessarily contain a phospholipid

surface modifier and may also contain a *second* surface modifier such as a polysorbate. (See Parikh, col. 3, ll. 3-49 for discussion of “second surface modifier;” also see formulations of all examples in Parikh and entire document.). Accordingly, since Karan teaches against the use of *sodium* dantrolene formulation in a phospholipid (lecithin) composition and Parikh’s core teaching is that phospholipid *should* be used in the formulations, no skilled worker would be motivated to combine the references in a manner that could arrive at the presently claims *sodium dantrolene* invention. In addition, Parikh directly teaches against the presently claimed invention because it teaches that a phospholipid is required whereas the present invention does not require a phospholipid and even excludes the possibility in claims 3, 13, 118 and 119. Thus, the teachings of these two references cannot be reconciled or combined in a manner arriving at the presently claimed invention.

In view of the above, Applicants respectfully request withdrawal of the present rejection of the claims under 35 U.S.C. §103(a).

4. CONCLUSION

Applicants respectfully submit that pending claims 1, 3, 5, 19-22, 26, 85, 86, 88-91, 106, 107, 110, 112 and 117-119 of this application are now in condition for allowance, which action is respectfully requested. The Examiner is cordially invited to contact the undersigned to discuss any matter in this application.

Pursuant to 37 C.F.R. §1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. It is believed that no fees other than those paid concurrently are due in connection with the filing of this paper. However, should it be deemed that any other fee is due in connection with this paper, authorization is hereby given to charge such fee to Deposit Account No. 02-2275.

Respectfully submitted,

LUCAS & MERCANTI, LLP

Dated: July 27, 2009

CUSTOMER NO. 20311

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Attachment

EXHIBIT A

Docket No. 820.1020

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	ANDERSON, D.M. et al.
Serial No.	:	10/788,413
Filing Date	:	March 1, 2004
For	:	TREATMENT USING DANTROLENE
Examiner	:	WANG, Shengjun
Art Unit	:	1617

Proposed Claim Amendments

Commissioner for Patents
Washington, DC 20231

June 16, 2009

TO: Examiner Shengjun Wang

The proposed claims more narrowly encompass the commercial embodiments of the invention.

A “clean” listing of claims showing the proposed amendment of the claims begins on page 2 of this paper, for convenience.

A “marked-up” listing of claims showing the proposed amendment of the claims begins on page 12 of this paper.

Proposed Amendments to the Claims: CLEAN VERSION

This listing of claims would replace all prior versions, and listings, of claims in this application:

“Clean” Listing of Proposed Claims:

1. **(Proposed Amendment)** A safe for injection, low volume formulation of dantrolene sodium, for administration to mammals, comprising:

dantrolene sodium at a concentration in the range of 30 - 80 mg/ml or in the range of 10 – 60 mg/ml;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol; and
water as a liquid carrier,

wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

2. **(Withdrawn; Proposed Cancellation)**

3. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein the formulation consists essentially of:

dantrolene sodium at a concentration in the range of 30 - 80 mg/ml or in the range of 10 – 60 mg/ml;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol; and
water as a liquid carrier,

wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

4. (Withdrawn; **Proposed Cancellation**)

5. (**Proposed Amendment**) The safe for injection low volume formulation of claim 1, wherein the dantrolene sodium is the primary modulator of intracellular calcium present in the formulation.

6. (**Proposed Cancellation**)

7. (**Proposed Cancellation**).

8. (**Proposed Cancellation**).

9. (**Proposed Cancellation**)

10. (**Proposed Cancellation**)

11. (Canceled)

12. (**Proposed Amendment**) The safe for injection, low volume formulation of claim 1, further comprising polyvinylpyrrolidone (PVP).

13. (**Proposed Amendment**) The safe for injection, low volume formulation of claim 12, consisting essentially of:

dantrolene sodium at a concentration in the range of 30 - 80 mg/ml or in the range of 10 - 60 mg/ml;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol;

polyvinylpyrrolidone (PVP); and

water as a liquid carrier,

wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

14. **(Proposed Cancellation)**

15. (Withdrawn; **Proposed Cancellation**)

16. (Withdrawn; **Proposed Cancellation**)

17. (Withdrawn; **Proposed Cancellation**)

18. **(Proposed Cancellation)**

19. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein at least 95% of the dantrolene sodium particles in said liquid carrier are no more than 0.8 microns in diameter.

20. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein at least 95% of the dantrolene sodium particles in said liquid carrier are no more than 0.45 microns in diameter.

21. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein no particles of dantrolene sodium in said liquid carrier are more than 2 microns in diameter.

22. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein the compound is mannitol and the formulation comprises no more than 30 milligrams of mannitol per milligram of dantrolene.

23. **(Proposed Amendment)** A dry formulation of dantrolene sodium which, upon addition of water, produces a safe for injection, low volume formulation of dantrolene sodium, for administration to mammals, comprising:

dantrolene sodium in dry form;

a water-soluble polysorbate in dry form; and

a compound in dry form selected from the group consisting of sorbitol and mannitol, said formulation being reconstitutable by water to a concentration of dantrolene in the range of 30 - 80 mg/ml or in the range of 10 - 60 mg/ml to provide a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration and ready for injection.

24. **(Proposed Amendment)** The dry formulation of claim 23, wherein at least 95% of the dantrolene sodium particles are no more than 0.8 microns in diameter.

25. **(Proposed Amendment)** The dry formulation of claim 23, wherein the compound is mannitol and the formulation comprises no more than 30 milligrams of mannitol per milligram of said dantrolene.

26. **(Proposed Cancellation)** The dry formulation of claim 23, further comprising polyvinylpyrrolidone (PVP).

27. (Withdrawn; **Proposed Cancellation**)

28. (Withdrawn; **Proposed Cancellation**)

29. (Withdrawn **Proposed Cancellation**)

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30-74. (Canceled)

75. (Withdrawn; **Proposed Cancellation**)

76. (Withdrawn; **Proposed Cancellation**)

77. (Withdrawn; **Proposed Cancellation**)

78. (Withdrawn; **Proposed Cancellation**)

79-80. (Canceled)

81. (Withdrawn; **Proposed Cancellation**)

82. (Canceled)

83. (**Proposed Cancellation**)

84. (**Proposed Cancellation**)

85. (**Proposed Amendment**) The composition of claim 1, wherein said water soluble polysorbate has a solubility of 5 mg/ml or greater.

86. (**Proposed Amendment**) The composition of claim 1, further comprising a medicament different from said dantrolene sodium.

87. **(Proposed Cancellation)**

88. **(Proposed Amendment)** The composition of claim 1, comprising a quantity of liquid which permits administration of a therapeutic dose of dantrolene by injection of said composition to a patient.

89. (Previously presented) The composition of claim 88 wherein said quantity ranges from 3 - 150 milliliters.

90. (Previously presented) The composition of claim 88 wherein said quantity is 10 milliliters or less.

91. (Previously presented) The composition of claim 88 wherein said quantity is 5 milliliters or less.

92. (Canceled)

93. **(Proposed Cancellation)**

94. **(Proposed Cancellation)**

95. (Canceled)

96. **(Proposed Cancellation)**

97. **(Proposed Cancellation)**

98. **(Proposed Cancellation)**

99. **(Proposed Cancellation)**

100. **(Proposed Cancellation)**

101. **(Proposed Cancellation)**

102. **(Proposed Cancellation)**

103. **(Proposed Amendment)** A method for preparing a safe for injection, low volume formulation of dantrolene sodium, consisting essentially of the step of:

combining a dry formulation comprising:

dantrolene sodium in dry form;

a water-soluble polysorbate in dry form; and

a compound in dry form selected from the group consisting of sorbitol and mannitol,

said dry formulation being reconstitutable by water to provide a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration,

with water to form a liquid formulation that is a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration, and in which the dantrolene sodium is present in a concentration wherein 3 to

150 milliliters of the liquid formulation provides approximately 500 milligrams of dantrolene sodium,

said combining step being performed according to one or more of the following: (a) by a single person, (b) by hand shaking, (c) in a single vial or syringe, and (d) in one minute or less,

and whereupon said combining, the liquid formulation is ready for injection.

104. **(Proposed Amendment)** A method for preparing a safe for injection, low volume formulation of dantrolene sodium, consisting essentially of the step of:

combining a dry formulation comprising:

dantrolene sodium in dry form;

a water-soluble polysorbate in dry form; and

a compound in dry form selected from the group consisting of sorbitol and mannitol,

said dry formulation being reconstitutable by water to provide a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration, with 3 to 150 milliliters of water to form a liquid formulation that is a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration, and in which the dantrolene sodium is present in a concentration wherein 3 to 150 milliliters of the liquid formulation provides approximately 500 milligrams of dantrolene sodium;

whereupon said combining, the liquid formulation is ready for injection.

105. **(Proposed Amendment)** The method of claim 104 wherein said combining step is performed according to one or more of the following: (a) by hand shaking, (b) by vortexing, and (c) in one minute or less.

106. (Previously presented) The safe for injection, low volume formulation of claim 1 comprising a dose of 250 - 300mg dantrolene sodium and which can be safely administered to a human by a single bolus injection in less than one minute.

107. (Previously presented) The safe for injection, low volume formulation of claim 106 comprising a dose of 250 mg of dantrolene sodium.

108. **(Proposed Amendment)** The dry formulation of claim 23 present in a single vial to be reconstituted in said vial with 10 ml or less water into a suspension which is safe for injection and which has a concentration of sodium dantrolene of 30 to 80 mg/ml.

109. **(Proposed Amendment)** The dry formulation of claim 108 which after reconstitution can be safely administered to a human by a single bolus injection in less than one minute.

110. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein said dantrolene sodium is present at 50 mg/ml.

111. **(Proposed Amendment)** The dry formulation of claim 23, wherein the formulation is reconstitutable by water to a concentration of dantrolene of 50 mg/ml to provide a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration.

112. **(Proposed Cancellation)**

113. **(Proposed Cancellation)**

114. **(Proposed Cancellation)**

115. **(Proposed Cancellation)**

116. **(Proposed Cancellation)**

117. **(Proposed New)** A safe for injection, low volume liquid formulation of dantrolene sodium for administration to mammals, comprising:

dantrolene sodium at a concentration wherein 3 to 150 milliliters of the liquid formulation provides approximately 500 milligrams of the sodium dantrolene;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol; and

water as a liquid carrier, wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

Proposed Amendments to the Claims: MARKED-UP VERSION

This listing of claims would replace all prior versions, and listings, of claims in this application:

“Marked-Up” Listing of Proposed Claims:

1. **(Proposed Amendment)** A safe for injection, low volume formulation of dantrolene sodium, ~~or salts or analogues thereof~~, for administration to mammals, comprising:

a medicament which includes dantrolene sodium at a concentration in the range of 30 - 80 mg/ml or in the range of 10 – 60 mg/ml; or one or more salts or analogues thereof;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol; and
water as a liquid carrier, said medicament being dissolved or dispersed in said liquid
~~earlier, said medicament being present in a concentration wherein 3 to 150 milliliters of liquid~~
~~earlier provides approximately 500 milligrams of medicament;~~

wherein said dantrolene sodium and water are present together as a colloidal dispersion
of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average
diameter, and

wherein the formulation is safe for intravenous administration.

2. **(Withdrawn; Proposed Cancellation)**

3. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein ~~said medicament includes dantrolene in its salt form wherein a counterion to a dantrolene anion is selected from the group consisting of potassium, sodium, ammonium, calcium and magnesium~~ the formulation consists essentially of:

dantrolene sodium at a concentration in the range of 30 - 80 mg/ml or in the range of 10 – 60 mg/ml;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol; and
water as a liquid carrier,

wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

4. (Withdrawn; **Proposed Cancellation**)

5. (**Proposed Amendment**) The safe for injection low volume formulation of claim 1₁ wherein ~~the dantrolene sodium or one or more salts or analogues thereof~~ is the primary modulator of intracellular calcium present in ~~said medicament~~ the formulation.

6. (**Proposed Cancellation**)

7. (**Proposed Cancellation**).

8. (**Proposed Cancellation**).

9. (**Proposed Cancellation**)

10. (**Proposed Cancellation**)

11. (Canceled)

12. (**Proposed Amendment**) The safe for injection, low volume formulation of claim 1₁ further comprising ~~a stabilizer~~ polyvinylpyrrolidone (PVP).

13. (**Proposed Amendment**) The safe for injection, low volume formulation of claim 4 12, consisting essentially of: ~~wherein said medicament and said liquid carrier are present together in a solution~~

dantrolene sodium at a concentration in the range of 30 - 80 mg/ml or in the range of 10 – 60 mg/ml;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol;

polyvinylpyrrolidone (PVP); and

water as a liquid carrier,

wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

14. **(Proposed Cancellation)**

15. (Withdrawn; **Proposed Cancellation**)

16. (Withdrawn; **Proposed Cancellation**)

17. (Withdrawn; **Proposed Cancellation**)

18. **(Proposed Cancellation)**

19. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein at least 95% of the dantrolene sodium particles ~~of medicament~~ in said liquid carrier are no more than 0.8 microns in diameter.

20. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein at least 95% of the dantrolene sodium particles ~~of medicament~~ in said liquid carrier are no more than 0.45 microns in diameter.

21. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1₃ wherein no particles of dantrolene sodium medicament in said liquid carrier are more than 2 microns in diameter.

22. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein the compound is mannitol and the formulation comprises ~~comprising~~ no more than 30 milligrams of mannitol per milligram of dantrolene.

23. **(Proposed Amendment)** A dry ~~powder~~ formulation of dantrolene sodium which, upon addition of water, ~~a liquid carrier~~, produces a safe for injection, low volume formulation of dantrolene sodium, for administration to mammals, comprising:

dantrolene sodium in dry form;
a water-soluble polysorbate in dry form; and
a compound in dry form selected from the group consisting of sorbitol and mannitol,
said formulation being reconstitutable by water to a concentration of dantrolene in the
range of 30 - 80 mg/ml or in the range of 10 - 60 mg/ml to provide a colloidal dispersion of
dantrolene sodium particles less than about 2 microns in average diameter in the water that
a medicament which includes dantrolene or salts or analogues thereof which has physical
characteristics such that when combined with a liquid carrier forms a solution or suspension with
said medicament being present in a concentration wherein 3 to 50 milliliters of liquid carrier
provides approximately 500 milligrams of medicament;
wherein the formulation is safe for intravenous administration and ready for injection.

24. **(Proposed Amendment)** The dry ~~powder~~ formulation of claim 23₁ wherein ~~said physical~~ characteristics include a drug particle size of less than 0.8 microns and a surface chemistry that ensures dispersibility at least 95% of the dantrolene sodium particles are no more than 0.8 microns in diameter.

25. **(Proposed Amendment)** The dry ~~powder~~ formulation of claim 23, wherein the compound is mannitol and the formulation comprises ~~comprising~~ no more than 30 milligrams of mannitol per milligram of said dantrolene.

26. **(Proposed Cancellation)** The dry ~~powder~~ formulation of claim 23, ~~wherein said medicament includes dantrolene sodium~~ further comprising polyvinylpyrrolidone (PVP).

27. (Withdrawn; **Proposed Cancellation**)

28. (Withdrawn; **Proposed Cancellation**)

29. (Withdrawn **Proposed Cancellation**)

30-74. (Canceled)

75. (Withdrawn; **Proposed Cancellation**)

76. (Withdrawn; **Proposed Cancellation**)

77. (Withdrawn; **Proposed Cancellation**)

78. (Withdrawn; **Proposed Cancellation**)

79-80. (Canceled)

81. (Withdrawn; **Proposed Cancellation**)

82. (Canceled)

83. (**Proposed Cancellation**)

84. (**Proposed Cancellation**)

85. (**Proposed Amendment**) The composition of claim 1, ~~83~~ wherein said water soluble polysorbate surfactant has a solubility of 5 mg/ml or greater.

86. (**Proposed Amendment**) The composition of claim 1, ~~83~~ further comprising a ~~second~~ medicament different from said dantrolene ~~or salt of dantrolene medicament~~ sodium.

87. (**Proposed Cancellation**)

88. (**Proposed Amendment**) The composition of claim 1, ~~83~~ further comprising a quantity of liquid which permits administration of a therapeutic dose of dantrolene by injection of said composition to a patient.

89. (Previously presented) The composition of claim 88 wherein said quantity ranges from 3 - 150 milliliters.

90. (Previously presented) The composition of claim 88 wherein said quantity is 10 milliliters or less.

91. (Previously presented) The composition of claim 88 wherein said quantity is 5 milliliters or less.

92. (Canceled)

93. **(Proposed Cancellation)**

94. **(Proposed Cancellation)**

95. (Canceled)

96. **(Proposed Cancellation)**

97. **(Proposed Cancellation)**

98. **(Proposed Cancellation)**

99. **(Proposed Cancellation)**

100. **(Proposed Cancellation)**

101. **(Proposed Cancellation)**

102. **(Proposed Cancellation)**

103. **(Proposed Amendment)** A method for preparing a safe for injection, low volume formulation of dantrolene sodium, or salts or analogues thereof, comprising consisting essentially of the step of:

combining a ~~medicament which includes dantrolene or one or more salts or analogues thereof~~ dry formulation comprising:

dantrolene sodium in dry form;

a water-soluble polysorbate in dry form; and

a compound in dry form selected from the group consisting of sorbitol and mannitol,

said dry formulation being reconstitutable by water to provide a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration,

with water to form a liquid formulation that is a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration, and in which the dantrolene sodium is ~~a liquid carrier and dissolving or dispersing said medicament in said liquid carrier, said medicament being present in a concentration wherein 3 to 150 milliliters of the liquid formulation~~ earlier provides approximately 500 milligrams of dantrolene sodium, medicament,

said combining step being performed according to one or more of the following: (a) by a single person, (b) by hand shaking, (c) in a single vial or syringe, and (d) in one minute or less,

wherein the formulation is safe for intravenous administration and whereupon said combining, the liquid formulation is ready for injection.

104. **(Proposed Amendment)** A method for preparing a safe for injection, low volume formulation of dantrolene sodium, or salts or analogues thereof, comprising consisting essentially of the step of:

combining a ~~medicament which includes dantrolene or one or more salts or analogues thereof~~ dry formulation comprising:

dantrolene sodium in dry form;
a water-soluble polysorbate in dry form; and
a compound in dry form selected from the group consisting of sorbitol and
mannitol,

said dry formulation being reconstitutable by water to provide a colloidal
dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the
water that is safe for intravenous administration, with 3 to 150 milliliters of water to form a
liquid formulation that is a colloidal dispersion of dantrolene sodium particles less than about 2
microns in average diameter in the water that is safe for intravenous administration, and in which
the dantrolene sodium is a liquid carrier and dissolving or dispersing said medicament in said
liquid carrier, said medicament being present in a concentration wherein 3 to 150 milliliters of
the liquid formulation carrier provides approximately 500 milligrams of dantrolene sodium
medicament,

wherein the formulation is safe for intravenous administration whereupon said
combining, the liquid formulation is ready for injection.

105. **(Proposed Amendment)** The method of claim 104 wherein said combining step is performed according to one or more of the following: (a) ~~by a single person,~~ (b) by hand shaking, (b) by vortexing, (c) ~~in a single vial or syringe,~~ and (d) (c) in one minute or less.

106. (Previously presented) The safe for injection, low volume formulation of claim 1 comprising a dose of 250 - 300mg dantrolene sodium and which can be safely administered to a human by a single bolus injection in less than one minute.

107. (Previously presented) The safe for injection, low volume formulation of claim 106 comprising a dose of 250 mg of dantrolene sodium.

108. **(Proposed Amendment)** The dry ~~powder~~ formulation of claim 23 present in a single vial to be reconstituted in said vial with 10 ml or less ~~sterile~~ water into a suspension which is safe for injection and which has a concentration of sodium dantrolene of 30 to 80 mg/ml.

109. **(Proposed Amendment)** The dry ~~powder~~ formulation of claim 108 which after reconstitution can be safely administered to a human by a single bolus injection in less than one minute.

110. **(Proposed Amendment)** The safe for injection, low volume formulation of claim 1, wherein said dantrolene sodium ~~medicament~~ is present at 50 mg/ml.

111. **(Proposed Amendment)** The dry ~~powder~~ formulation of claim 23, wherein the ~~medicament~~ on being combined with liquid carrier is present at 50 mg/ml formulation is reconstitutable by water to a concentration of dantrolene of 50 mg/ml to provide a colloidal dispersion of dantrolene sodium particles less than about 2 microns in average diameter in the water that is safe for intravenous administration.

112. **(Proposed Cancellation)**

113. **(Proposed Cancellation)**

114. **(Proposed Cancellation)**

115. **(Proposed Cancellation)**

116. **(Proposed Cancellation)**

117. **(Proposed New)** A safe for injection, low volume liquid formulation of dantrolene sodium for administration to mammals, comprising:

dantrolene sodium at a concentration wherein 3 to 150 milliliters of the liquid formulation provides approximately 500 milligrams of the sodium dantrolene;

a water-soluble polysorbate;

a compound selected from the group consisting of sorbitol and mannitol; and

water as a liquid carrier, wherein said dantrolene sodium and water are present together as a colloidal dispersion of dantrolene sodium particles in the water,

wherein the dantrolene sodium particles are less than about 2 microns in average diameter, and

wherein the formulation is safe for intravenous administration.

REMARKS

It is proposed to cancel presently elected claims 4, 6-10, 14, 18, 83, 84, 87, 93, 94, 96-102 and 113-116 *and* also cancel presently withdrawn claims 2, 4, 15-17, 27-29, 75-78 and 81.

It is proposed to amend claims 1, 3, 5, 12, 13, 19-26, 85, 86, 88, 103-105 and 108-112, as shown in the listing of proposed claims beginning on page 2 of this paper. The proposed amendments more narrowly limited the claims to the commercial embodiments of the invention.

Pursuant to the proposed amendments of the claims, claims 1, 3, 5, 19-26, 85, 86, 88-91, and 103-112 will be pending and under examination.

Support for the amendment of each of claims 1 and 3 is found in the originally filed specification ("o/f/s") as follows: Support for 30-80 mg/ml at page 21, ll. 4-8 of the o/f/s. Support for 10-60 mg/ml concentration limitation found in now-canceled, originally filed Claim 6). Support for the polysorbate limitation is found in claim 101. Support for mannitol or sorbitol limitation is found at page 19, ll. 22-24 of o/f/s.

Claim 5 is amended to agree with its base claim 1.

Support for the amendment of claim 12 (PVP limitation) is found at page 15, ll. 4-5 of the o/f/s. Support for the amendment of claim 13 is found at page 15, ll. 4-5 of the o/f/s and the same aforementioned support for the amendment of claims 1 and 3.

Claims 19-21 are amended to agree with the language of base claim 1. Claim 22 is amended to more clearly recite the invention.

Support for the amendment of claim 23 is found as follows: Support at page 2, ll. 12-15 of the o/f/s/ (dry form limitation). Support in claim 101 (polysorbate limitation). Support at page 19, ll. 22-24 of o/f/s (mannitol or sorbitol limitation). Support in claims 8, 108 and 109 and at page 21 ll. 4-8 of o/f/s (reconstitutable by water limitation) Support for 30-80 mg/ml at page 21, ll. 4-8 of the o/f/s. Support for 10-60 mg/ml concentration limitation found in now-canceled, originally filed Claim 6). Support at page 2, ll. 12-15 of the o/f/s/ (particle size limitation). Support in originally filed claim 7 and also at page 2, ll. 12-15 of the o/f/s/ (colloidal dispersion Support in now-cancelled dependent claim 112 (ready-for injection limitation).

Support for the amendment of claim 24 is found at page 43, ll. 23-24 of the o/f/s.

Claim 25 is amended to more clearly recite what Applicants regard as the invention. Each of claims 85, 86 and 88 is amended to agree with amended claim 1 and the dependency of claim 88 is changed to be dependent on claim 1.

Support for the amendment of each of claims 103 and 104 is found as follows: Support at page 2, ll. 12-15 of the o/f/s/ (dry form limitation). Support in claim 101 (polysorbate limitation). Support at page 19, ll. 22-24 of o/f/s (mannitol or sorbitol limitation). Support in claims 8, 108 and 109 and at page 21 ll. 4-8 of o/f/s (reconstitutable by water limitation) Support for 30-80 mg/ml at page 21, ll. 4-8 of the o/f/s. Support for 10-60 mg/ml concentration limitation found in now-canceled, originally filed Claim 6). Support at page 2, ll. 12-15 of the o/f/s/ (particle size limitation). Support in originally filed claim 7 and also at page 2, ll. 12-15 of the o/f/s/ (colloidal dispersion). Support for the ready for injection limitation is found in now-canceled dependent claim 116.

Support for the amendment of claim 105 is found at page 21, ll. 10-11 of the o/f/s.

Each of claims 108-111 is amended to more clearly recite what Applicants regard as the invention.

Support for new claim 117 is found in prior version of claim 1 (concentration limitation), prior claim 101 (polysorbate limitation), page 19, ll. 22-24 of the originally filed specification (sorbitol or mannitol limitation), in claim 8 and at page 21 ll. 4-8 of the o/f/s (water as carrier), originally filed claim 7 and also at page 2, ll. 12-15 (colloidal dispersion), and page 2, ll. 12-15 of the o/f/s (diameter limitation)

Applicants respectfully submit that the proposed claim amendments will place the application in condition of allowance.

Respectfully submitted,

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Dated: June 16, 2009

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